REMARKS

Applicants gratefully acknowledge telephonic conversation with the Examiner on July 11, 2006.

Claims 36 - 41 and 44 are withdrawn pursuant to Examiner's imposed requirement. Claims 7, 22 -25 stand withdrawn and claims 1-6, 8, 10- 21, 26 – 35, as well as claims 48 - 51 stand cancelled. Claims 42, 43, 45, 46 and 47 are now pending. The amendments are fully supported by the claims as filed and no new matter is believed to have been added.

Claims 42-43, 45 and 50-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 42-43 and 48-51 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 42-43, 45 and 48-51 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-51 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 -787).

Claims 42 and 43 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 -787).

The above amendments and the following remarks have addressed all the grounds for rejection and/or objection or have otherwise rendered them moot. Applicants respectfully request the Examiner reconsider all outstanding rejections, and that they be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 42-43, 45 and 50-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that the claims are generic and drawn to an unidentified polynucleotide encoding a plant fusion polypeptide, and encompass more than just timothy grass allergens. Applicants disagree and traverse as follows.

The text of the Remarks section of the Response and Amendments filed in response to the December 23, 2005, Office Action are incorporated here in its entirety. By copiously citing to portions of the specification in said prior response, Applicants contended that their disclosure enabled much more than fusion proteins of timothy grass pollen allergens. At the very least, it enabled fusion proteins of plant allergens whose sequences were already known as at the filing of the instant application. Applicants do not believe that the law requires them to list the sequences of all plant allergens whose sequences were already in the public domain as at the time of filing this application. Further, Applicants are absolutely under no obligation, as a matter of law, to burden the instant Application with subject matter which is within easy and ready reach of one of skill in the art to which this invention pertains as at the time of filing the instant Application.

It is the Examiner's contention that Applicants have attempted to describe the species of fusion allergens encompassed by the claims by functional, rather than structural limitations, and that that is per se insufficient written description to support product claims. Applicants believe that the Examiner has still failed to grasp the essential nature of their invention. Without meaning to narrow the scope of the invention, Applicants assert that what they have invented is a heuristic method which they validated by use of timothy grass pollen allergens. Heuristic implies a method of making a discovery, which the Examiner can appreciate, is in and of its self, inventive. In order words, the instant invention has taught how to rapidly determine suitable

immunotherapeutic agents without resorting to experimentally intensive and costly structural and epitopic mapping of putative agents. In other words, the heuristic methodology of the present invention totally obviates rigorous structural characterization of putative allergens and it is that same subject matter which the invention obviated that the Examiner deems a requirement for patentability.

Briefly, plant hybrid fusion allergens or fragments thereof which upon injection into an immunological model induce blocking antibodies and have less allergenic activity compared to the component wild-type allergens are encompassed by the invention. Until now, no one has taught or thought that fusion proteins of allergens can be used as immunotherapeutic agents. The Examiner insists that this functional attribute does not adequately define the structure of the immunotherapeutic agents of the invention. Applicants believe that having used timothy grass pollen allergens to validate their hypothesis and opened up a whole new vistas in immunotherapy – namely use of hybrid fusion allergens or fragments thereof, that one of skill in the art knows that the current inventors have in their possession, as at the filing date of the present invention, all known plant allergens which upon being fused exhibit the easily verifiable and desirable functional characteristics. Applicants still believe that the appropriate inquiry is what the Applicants had possession of as at the filing date and not what sequences were disclosed in the application, the making of fragments and modifications and such being matters within easy and ready reach of skilled artisans in the field.

For instance, crude and uncharacterized allergen extracts are used to sensitize a patient's immune system in a manner that makes it unnecessary to try to envisage the structure of the allergens in any particular batch of extracts. And yet, a patent may issue to an allergen extract, prepared by whatever inventive means without requiring that the extract be fully structurally characterized. Similarly fusion proteins or fragments thereof that elicit high blocking antibodies production according to the present invention can be

claimed and used as immunotherapeutic agent and the utility of the invention will in no way be diminished by failure to specify the epitopic attributes of the agent.

Nevertheless, to advance the prosecution of this Application and with full reservation of right to pursue the currently surrendered subject matter in separate Applications, and pursuant to telephonic conversations with the Examiner, Applicants have restricted their claims to timothy grass pollen allergens. It is believed that this ground for rejection has been rendered moot and it is respectfully requested that it be withdrawn.

Claims 42-43 and 48-51 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that there is no teaching of a hybrid polypeptide comprising the generic components which induce an in vivo antibody response in any host. Applicants respectfully disagree.

The validity of the present methodology of discovering immunotherapeutic agents have been verified by use of timothy grass pollen allergens. There is absolutely no scientific reason to believe that this methodology will not work with any other class of allergens. The methodology of the present invention works for mechanistic reasons that can only be the subject of much speculation and surprise to the scientific community. As might be expected, the fusion of two proteins is expected to impact the secondary and tertiary structures of the component proteins and as such may be expected to affect their epitopic configuration. And rather than trying to discover the exact epitopic configuration, this application concerns itself with hybrid fusion polypeptides of whatever epitopic configuration that elicit blocking antibody production and have reduced antigenicity compared to the respective wild type components. Applicants believe that it is clear and manifest error on the part of the Examiner to insist that

Applicants must disclose a universal epitopic configuration in order to be entitled to generically claim the immunotherapeutic agents encompassed by the present invention.

Again, in order to advance the prosecution of this Application, the claims have been restricted to timothy grass pollen allergens thus again obviating this ground for rejection. It is respectfully requested that this ground for rejection be withdrawn.

Rejections 35 U.S.C. § 112, second paragraph

Claims 42-43, 45 and 48-51 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that there is insufficient antecedent basis for "the respective wild-type allergens" in the claims.

Applicants have amended the claims in some cases to obviate the use of that term and in other cases to try to impact more clarity to the claims. It should be pointed out that the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. MPEP 2173.05(e). As used here, "the respective wild-type allergens" in relation to a fusion protein clearly and precisely conveys to one of skill in the art that the fusion protein inherently consists of the wild-type allergens. As such, it is respectfully requested that this ground for rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 45-51 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 -787). According to the Examiner, Ball et al. teach that the major grass pollen Phl p1 can be part of a hybrid or fusion polypeptide but does not specifically recite using another plant allergenic protein within the hybrid polypeptide. To cure the

deficiency in Ball, the Examiner asserts that Vrtala et al., teach that DNA coding for three major timothy grass pollen allergens representing group I (Phl p1), group II (Phl p2) and group V(Phl p5) was known. Therefore, concludes the Examiner, "it would have been prima facie obvious at the time of applicants' invention to modify the plant polypeptide as taught by Ball et al., to include a different plant allergen as taught by Vrtala et al., to create a hybrid plant fusion allergen wherein said allergen is a fusion protein of two or more timothy grass pollen allergens." Applicants respectfully disagree and traverse as follows.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the combination should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir, 1988). In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. As a matter of law, therefore, the mere fact that the prior art could be so modified would not make the modification obvious unless the prior art suggested the desirability of the modification. In re Laskowski, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989).

The Ball et al. reference is equivalent to U.S. Patent No. 6,008,340. Applicants refer the Examiner to the following excerpt which captures the entire teaching of Ball et al. with respect to fusion proteins of Phl p1 epitopes and expressible polypeptides.

> A fourth aspect of the invention is a recombinant or synthetic protein or polypeptide displaying the antigenicity of a Phl p I epitope, in particular comprising as an essential part a Phl p I epitope of at least one of the sequences set out in SEQ ID NOS: 5, 7 and 9-28. The protein or polypeptides may be fused to an additional polypeptide, such as beta

galactosidase, GST or lambda cII protein or **any other polypeptide that can be expressed as a fusion protein** in prokaryotic or eukaryotic cells. U.S. 6,008,340 Col. 2, ln 64 -67; Col. 3, ln 1-6.

Per the above excerpt, Ball et al. teach the expression of Phl p1 epitopes fused with expressible proteins in order to amplify the expression of the Phl p1 epitope and to aid in downstream isolation, purification and homogenization of the expressed protein. There is no suggestion, teaching, motivation, express or implied in the Ball et al. disclosure that the fusion protein of Phl p1 epitopes and expressible proteins could so re-configure the epitopic configuration of the allergen that the entire fusion protein can be used as an immunotherapeutic agent. In fact, it would be incongruous to assume so. The entire purpose of the Ball et al. reference is to isolate and use well defined epitopes of Phl p1 as immunotherapeutic agents for the ostensible purpose of departing from the prior use of ill-defined pollen extracts as desensitization agents. Ball et al. in no way taught or suggested administering Phl p1 epitopes, fused of all proteins, with bacterial or viral expression conjugants. As the Examiner can imagine, such expression conjugants can trigger anaphylactic reactions when administered fused with allergens. In fact, Ball et al. teaches away from administering any other allergen other than well defined epitopes of Phl p1.

Ball et al. fusion protein of Phl p1 epitopes along with expressible proteins or expression conjugants in no way suggests the desirability of using hybrid fusion allergens as immunotherapeutic agents. For that matter, the hybrid fusion allergens of the present invention may be fused with expressible proteins in order to amplify the expression of the hybrid fusion allergens and facilitate the isolation, purification and homogenization of those allergens. That technology of amplifying expression of desirable proteins by fusing them with expressible proteins is old and well known. The Examiner is referred to the following teaching from the Ball et al. patent.

The Phl p I epitope encoded by clone 98 was expressed as a beta - galactosidase fusion protein in liquid culture (**Huynh et al., 1985**) and was

affinity purified using an anti-beta-galactosidase affinity column. (Promega, Maddison, USA) as described (Vrtala et al., 1993a). U.S. 6,008,340 Col. 5, ln 59 -65.

The Huynh et al., (1985) reference at least stands for the teaching that the fusion of proteins with expressible proteins is not new and Ball et al. taught no more than the fusion of Phl p1 epitopes with expressible proteins merely to amplify the expression of and to aid in isolation of proteins of therapeutic interest. .

Prior to the current invention, no one has taught or suggested that the fusion of hybrid allergens can produce immunotherapeutic agents more desirable than the respective component allergens. That such is the case was indeed a surprise to the inventors who are leading researchers in this area. The Rule 132 declaration submitted herewith affirm the inventor's surprise that fusion proteins of naturally occurring allergens can be used as immunotherapeutic agents and exhibit increased immunogenicity. That surprising discovery at least negates the finding of obviousness on the basis of the Ball et al. and Vrtala et al. combination.

On the basis of the foregoing, Applicants respectfully assert that the above combination is improper and that this ground for rejection should be withdrawn.

Claims 42 and 43 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 -787). Applicants respectfully assert that the foregoing considerations have rendered this rejection moot and request that it be accordingly withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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